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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Alberto Martin

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12/30/2009

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EXAMINER

BURKHART, MICHAEL D

ART UNIT

PAPER NUMBER

1633

MAIL DATE

DELIVERY MODE

12/30/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/501,628	Applicant(s) MARTIN ET AL.	
	Examiner Michael Burkhart	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 November 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9, 13, 15, 18-25, 58, 97, 125 and 262-307 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-9, 13, 15, 18-25, 58, 97, 125 and 262-307 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>11/17/2009</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/17/2009 has been entered.

Information Disclosure Statement

The information disclosure statement filed 11/17/2009 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The IDS has been considered, but those references not supplied, or which are duplicates of references already of record, have been lined through.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6-9 13, 15, 19-22, 24-25, 58, 97, 125, 262-272, 276-284, and 287-307 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wabl et al (US 5,885,827, of record) in view of Muramatsu et al (Cell, 2000, pp. 553-563, of record) as evidenced by Martin et al (PNAS, 2002, of record). **This rejection is maintained for reasons made of record in the Office Actions dated 9/13/2007, 11/14/2008, 5/27/2009, and for reasons set forth below.**

Claims 5 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wabl et al (5,885,827, of record) and in view of Muramatsu et al (2000, of record) as evidenced by

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Martin et al (2002) as applied to claims 1-4, 6-9 13, 15, 19-22, 24-25, 58, 97, 125, 262-272, 276-284, and 287-307 above, further in view of Wang et al (US Patent Publication 2003/0119190, of record). **This rejection is maintained for reasons made of record in the Office Actions dated 9/13/2007, 11/14/2008, 5/27/2009, and for reasons set forth below.**

Claims 273, 274, and 275 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wabl et al (US 5,885,827, of record) and Muramatsu et al (Cell, 2000, of record) as evidenced by Martin et al (2002) as applied to claims 1-4, 6-9 13, 15, 19-22, 24-25, 58, 97, 125, 262-272, 276-284, and 287-307 above, and further in view of Griffiths (US 5,885,827, of record). **This rejection is maintained for reasons made of record in the Office Actions dated 9/13/2007, 11/14/2008, 5/27/2009, and for reasons set forth below.**

Claims 18, 285 and 286 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wabl et al (US 5,885,827, of record) and Muramatsu et al (Cell, 2000, of record) as evidenced by Martin et al (2002) as applied to claims 1-4, 6-9 13, 15, 19-22, 24-25, 58, 97, 125, 262-272, 276-284, and 287-307 above, and further in view of Hondo et al (US Patent 6,815,194, of record). **This rejection is maintained for reasons made of record in the Office Actions dated 9/13/2007, 11/14/2008, 5/27/2009, and for reasons set forth below.**

No amendments to the claims have been presented in the latest response.

Response to Arguments

Applicant's arguments filed 11/17/2009 have been fully considered but they are not persuasive. Applicants essentially assert: 1) Declarations submitted by Michael Neuberger (the Neuberger Declaration) and Matthew Scharff (the Scharff Declaration) are provided; 2) the Neuberger Declaration provides certain background information on SHM and CSR, that the two were thought to be different and distinct biological processes, but that some molecules were taught by the art to be involved in both SHM and CSR; 3) other molecules were proposed to have a role in SHM, and that AID was thought to be an APOBEC1-like protein due to homology; 4) the Neuberger Declaration offers a summation of the teachings of Muramatsu et al (2000) regarding the role of AID in CSR and SHM, and why the role of AID in both is surprising and unexpected; 5) AID was not reported as the key enzyme responsible for CSR and SHM, and the mechanism of AID was unknown; 6) the discovery that AID alone can induce CSR and SHM was surprising, and one of skill in the art would not have considered AID alone sufficient for SHM; 7) there was no reason to believe that AID directly induces DNA mutations; 8) the Scharff Declaration makes many of the same points as the Neuberger Declaration, but adds that the interpretation of results from knock-out mice can be difficult to interpret; 9) none of the references teaches that AID deaminates DNA, and the Examiner is wrong for relying upon inherency in this instance;

Regarding 1)-2), it is noted several references (Janeway et al, Poltoratsky et al) relied upon in the Neuberger Declaration have not been provided and therefore not considered. Applicants assert that the Poltoratsky reference is of record, but the reference of record does not

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correspond to that previously cited by page number (the reference of record appears to be a review article w. pages labeled "F27", etc.)

Regarding both Declarations, it is noted Mr. Scharff is listed as an inventor of the instant application, and declares he has a financial interest in the assignee of the instant invention. Mr. Neuberger also declares a financial interest in the assignee. Thus, both declarants have an interest in the outcome of this application.

Regarding 1) - 7), Muramatsu et al teach that the activity of AID ultimately resulted in changes to the DNA sequence of the IgM gene under study, (page 558, ¶ bridging first and second columns to page 559, Fig. 7B, and Table 1) Muramatsu et al postulate that AID may edit DNA directly (page 561, first column, first full ¶), in direct contrast to applicants assertions and opinions. Applicants are referred to the title of Muramatsu et al "Class Switch Recombination and Hypermutation Require Activation-Induced Cytidine Deaminase (AID), a Potential RNA Editing Enzyme"; the abstract; page 554, first column, third ¶; and page 561, first column, second full ¶, which states (emphasis added):

"Although we have provided the evidence that AID is the essential component for both CSR and hypermutation, their molecular mechanisms still remain to be solved."

The above passages do not resemble speculation, they are conclusions backed up by rather convincing experiments, in contrast to applicants assertions and opinions regarding the teachings of Muramatsu et al. Furthermore, the mechanism by which AID exerts its effects does not appear to be relevant. The mechanistic steps by which AID works are not steps performed by the skilled artisan, but rather a complex chemical reaction performed by the cell itself. It is enough

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to know that AID itself is a crucial component of the CSR and hypermutation pathways, there is no requirement that it act directly to mediate hypermutation as long as it is clear it is an essential component of the pathway (i.e. the results of Muramatsu et al). It may have been surprising that AID played such a prominent role in CSR and somatic hypermutation *before* Muramatsu et al did their experiments, but this ignores the teachings of the remainder of Muramatsu et al. Applicants ignore that Muramatsu et al also postulate that AID may directly edit DNA (see above).

Regarding 8), Muramatsu et al provide extensive teachings beyond using knockout mice regarding the involvement of AID in CSR and SHM for reasons of record: the interpretation of the Muramatsu et al knockout mice is not done in a vacuum. The results of an unrelated, non-claimed knock out genes (i.e. 5-HT, IGF-1) are hardly probative given the teachings of Muramatsu et al of record and discussed extensively.

Regarding 9), the combination of the references does not rely upon knowledge of the exact activity of AID in somatic hypermutation. The deamination of DNA is not a method step that the skilled artisan performs, rather, it is an inherent property of the use of the AID enzyme. Thus, the use of AID in the combination of Wabl and Muramatsu et al would have inherently deaminated DNA. Given the strong motivation already of record to combine the references, which does not require the knowledge of the exact activity of AID in the process of somatic hypermutation (see, e.g., pages 6-9 of the Office Action dated 11/14/2008), the fact that AID deaminates DNA directly (suggested by Muramatsu et al) does not render the instant invention non-obvious. The obvious combination of Wabl and Muramatsu et al would have inherently created deaminated DNA by using AID, and the obviousness rejection is not predicated on

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knowledge of the exact activity of AID. Further, see pages 6-9 of the Office Action dated 11/14/2008 for a discussion about how the teachings of the totality prior art do not rely upon the exact activity of AID to render the claimed invention obvious.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Conclusion

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period

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will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Burkhart whose telephone number is (571)272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Burkhart/
Primary Examiner, Art Unit 1633